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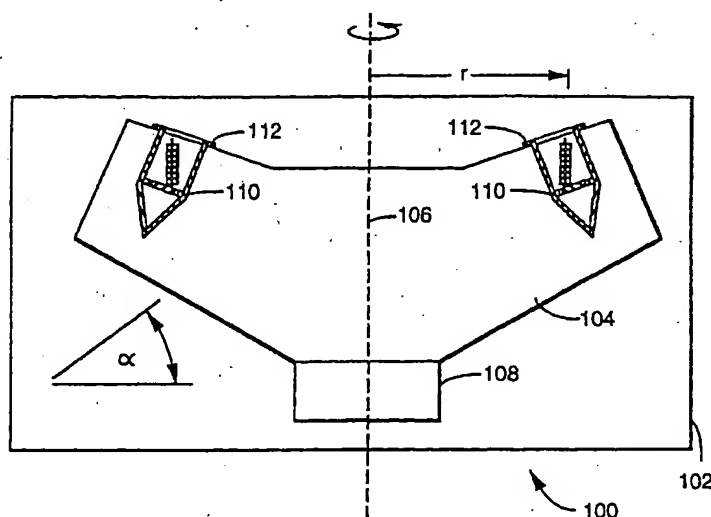
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(54) Title: SELECTIVE COATING OF MEDICAL DEVICES



(57) Abstract: Methods for coating different regions of an implantable device are disclosed. An embodiment of the method includes dipping a first portion of the implantable device into a first coating substance, and then centrifuging the implantable device to provide an even coating. Next, a second portion of the implantable device is dipped into a second coating substance, and the implantable device is again centrifuged, resulting in an even second coating. In another embodiment, a first coating substance is applied to an interior surface of a cylindrical implantable device, such as a stent or graft, and a second coating substance is applied to an exterior surface. A centrifuge step is performed so that the first coating substance is preferentially and uniformly applied on the interior surface of the implantable device and the second coating substance is preferentially and uniformly applied on the exterior surface of the implantable device.

SELECTIVE COATING OF MEDICAL DEVICES

5 FIELD OF THE INVENTION

The present invention relates to the coating of an implantable device. More specifically, this invention relates to a method for selective coating of an intraluminal implantable device, such as a stent or graft.

BACKGROUND

- 10 Occlusion of blood vessels reduces or blocks blood flow. During the course of atherosclerosis, for example, growths called plaques develop on the inner walls of the arteries and narrow the bore of the vessels. An emboli, or a moving clot, is more likely to become trapped in a vessel that has been narrowed by plaques. Further, plaques are common sites of thrombus formation. Together, these events increase the risk of heart attacks and strokes.
- 15 Traditionally, critically stenosed atherosclerotic vessels have been treated with bypass surgery in which veins removed from the legs, or small arteries removed from the thoracic cavity, are implanted in the affected area to provide alternate routes of blood circulation. More recently, implantable devices, such as synthetic vascular grafts and stents, have been used to treat diseased blood vessels.
- 20 Synthetic vascular grafts are macro-porous vessel-like configurations typically made of expanded polytetrafluoroethylene (ePTFE), polyethylene terephthalate (PET), polyurethane (PU), or an absorbable polymer. Grafts made of ePTFE or PET are very non-wetting materials when introduced into an aqueous environment, causing difficulty in impregnating the materials. In addition, grafts made of ePTFE or PET typically are
- 25 permanently implanted in the body, while grafts made of an absorbable polymer bioabsorb over time. A graft may be positioned into the host blood vessel as a replacement for a diseased or occluded segment that has been removed. Alternatively, a graft may be sutured to the host vessel at each end so as to form a bypass conduit around a diseased or occluded segment of the host vessel.

concentration to the target site, systemic administration of such medication may be used, which often produces adverse or toxic side effects for the patient. Local delivery is a desirable method of treatment, in that smaller total levels of medication are administered in comparison to systemic dosages, but are concentrated at a specific site. Therefore, local
5 delivery may produce fewer side effects and achieve more effective results.

One commonly applied technique for the local delivery of a therapeutic substance is through the use of a medicated implantable device, such as a stent or graft. Because of the mechanical strength needed to properly support vessel walls, stents are typically constructed of metallic materials. The metallic stent may be coated with a polymeric carrier, which is
10 impregnated with a therapeutic agent. The polymeric carrier allows for a sustained delivery of the therapeutic agent.

Various approaches have previously been used to join polymers to metallic stents, including dipping and spraying processes. In one technique, the stent is first formed in a flat sheet, placed in a solution of polyurethane, and heated for a short period of time. Additional
15 polyurethane solution is applied on top of the flat sheet, and the stent is again heated. This process produces a polyurethane film over the surface of the stent, and excess film is manually trimmed away. In one variation of this technique, microcapsules containing therapeutic agents are incorporated into the polyurethane film by adding the microcapsules to the polyurethane solution before heating.

20 In another technique, a solution is prepared that includes a solvent, a polymer dissolved in the solvent, and a therapeutic agent dispersed in the solvent. The solution is applied to the stent by spraying the solution onto the stent using an airbrush. After each layer is applied, the solvent is allowed to evaporate, thereby leaving on the stent surface a coating of the polymer and the therapeutic substance. Use of this spraying technique to apply a thick
25 coating may result in coating uniformity problems, so multiple application steps are sometimes used in an attempt to provide better coating uniformity.

In yet another coating technique, a solution of dexamethasone in acetone is prepared, and an airbrush is used to spray short bursts of the solution onto a rotating wire stent. The acetone quickly evaporates, leaving a coating of dexamethasone on the surface of the stent.

30 The above-described methods often have difficulty in applying an even coating on the stent surfaces. One common result when using these spraying or immersion processes is that

centrifuge step is performed so that the first coating substance is preferentially and uniformly applied on the interior surface of the implantable device and the second coating substance is preferentially and uniformly applied on the exterior surface of the implantable device.

5 Various embodiments of the described method enable highly viscous materials to be coated onto implantable devices. Viscous materials are not usually amenable to conventional coating methods such as dipping or spraying, because of the viscous material's propensity to accumulate in an uneven layer. However, the addition of a centrifugation step after dipping the implantable device in the viscous coating material can transform the uneven masses into a smooth, even coating.

10 Embodiments of the method also enable uniform coatings to be applied to implantable devices with improved repeatability, thereby improving coating uniformity between batches of implantable devices. With conventional manually-applied spray-coating techniques, operator error or inconsistency may result in different coating thicknesses between batches of stents. The centrifugation processes can reduce unwanted gross deposition of coating
15 substances and enable high reproducibility of the coating quality.

Embodiments of the method also enable multiple stents to be processed simultaneously. Unlike manually-applied airbrush coating methods, in which stents are coated individually or in small groups, large batches of stents can be simultaneously immersed in the coating solution, simultaneously rotated in the centrifuge device, and
20 simultaneously heated in an oven, thereby increasing throughput.

Embodiments of the method also may improve operator safety when coating implantable devices with hazardous materials. It is generally not desirable to spray coat an implantable device with toxic or radioactive coating substances, because of the increased exposure of the operator to the airborne hazardous coating substance. Dipping and
25 centrifuging the implantable device as described above can decrease the amount of handling required for the coating process, resulting in reduced environmental contamination.

Embodiments of the method may also mitigate defects due to handling of the implantable device. In conventional spray processes, the implantable device is held aloft using one or two clamps or fixtures while the coating substance is sprayed onto the device.
30 The point where these clamps contact the device may be masked from receiving the spray,

or any implantable device having a complicated architecture which is not amenable to standard coating.

The materials from which such stents are formed may include metals such as, but not limited to, stainless steel, "MP35N," "MP20N," elastin (Nitinol), tantalum, nickel-titanium alloy, platinum-iridium alloy, gold, magnesium, or combinations thereof. "MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from standard Press Steel Co., Jenkintown, PA. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum. The stent also may be made from virtually any biocompatible material, such as bioabsorbable or biostable polymers.

Vascular grafts may be used to replace, bypass, or reinforce diseased or damaged sections of a vein or artery. These grafts can be made from any suitable material including, but not limited to, highly open-pored materials such as polymers of expanded polytetrafluoroethylene (ePTFE) and polyethylene terephthalate (PET), or less porous materials such as polyurethanes, absorbable polymers, and combinations or variations thereof. Grafts may be formed using a lyophilization process. Polyurethanes from which the graft may be made include, but are not limited to, Biomer, BioSpan® polyurethane (manufactured by Polymer Technology Group, Berkeley, CA; referenced herein after as "BioSpan®"), and Elastion. Absorbable polymers from which the graft may be made include, but are not limited to, polycaprolactone (PCL), poly(lactic acid) (PLA), poly(glycolic acid) (PGA), polyanhydrides, polyorthoesters, polyphosphazenes, and components of extracellular matrix (ECM). In such an embodiment, additional interstices can be formed in the graft by any conventional methods known to one of ordinary skill in the art, including exposure of the graft to a laser discharge to form a pattern of pores.

In other embodiments, the implantable device to be coated is a covering for a self-expandable or balloon-expandable stent. This covering can be formed of materials similar to those from which the above-described graft may be formed.

Various types of coating substances may be applied to an implantable device in accordance with the present invention. In one embodiment, the coating substance includes a polymer loaded with a therapeutic substance. The terms "polymer," "poly," and "polymeric" as used herein mean the product of a polymerization reaction and are inclusive of

thereof. Examples of such antineoplastics and/or antimitotics include paclitaxel (e.g., TAXOL® by Bristol-Myers Squibb Co., Stamford, CT), docetaxel (e.g., Taxotere® from Aventis S.A., Frankfurt, Germany) methotrexate, azathioprine, actinomycin-D, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride (e.g., Adriamycin® from Pharmacia & Upjohn, Peapack, NJ), and mitomycin (e.g., Mutamycin® from Bristol-Myers Squibb Co., Stamford, CT). Examples of such antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapirost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin inhibitors such as Angiomax™ (Biogen, Inc., Cambridge, MA). Examples of such cytostatic or antiproliferative agents include angiopeptin, angiotensin converting enzyme inhibitors such as captopril (e.g., Capoten® and Capozide® from Bristol-Myers Squibb Co., Stamford, CT), cilazapril or lisinopril (e.g., Prinivil® and Prinzide® from Merck & Co., Inc., Whitehouse Station, NJ); calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug, brand name Mevacor® from Merck & Co., Inc., Whitehouse Station, NJ), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. An example of an antiallergic agent is permirolast potassium. Other therapeutic substances or agents that may be used include alpha-interferon, Trepidil antiplatelet (manufactured by DAITO Corporation, Japan; referenced herein after as "Trepidil"), genetically engineered epithelial cells, and dexamethasone. In yet other embodiments, the therapeutic substance is a radioactive isotope used in radiotherapeutic procedures. Examples of radioactive isotopes include, but are not limited to, phosphoric acid ($\text{H}_3\text{P}^{32}\text{O}_4$), palladium (Pd^{103}), cesium (Cs^{131}), and iodine (I^{125}).

While the preventative and treatment properties of the foregoing therapeutic substances or agents are well known to those of ordinary skill in the art, the substances or agents are provided by way of example and are not meant to be limiting. Other therapeutic substances are equally applicable for use with the disclosed embodiments. For example, while many of the herein-described therapeutic agents have been used to prevent or treat

Support 202 separates stent 206 from runoff reservoir 208, which is provided at the bottom of centrifuge container 112. Drainage openings 210 may be provided in support 202.

As can be seen in the embodiment shown in FIGs. 1-2, mandrel 204 is tilted such that when each centrifuge container 112 is mounted in centrifuge system 100, stents 206 are positioned such that their longitudinal axes are nearly parallel to axis of rotation 106. This may provide a more even coating on stents 206 after centrifugation. In alternative embodiments, mandrels 204 may have a different tilt angle relative to the central axes of centrifuge containers 112, or may have no tilt at all.

FIGs. 3 and 4 are flowcharts illustrating exemplary methods of coating an implantable device in accordance with an embodiment of the present invention. For the sake of example, the implantable device described with respect to FIGs. 1-4 is a stent, but the method also may be applied to various other implantable devices discussed above.

Referring to Figure 3, in act 301, a first coating is applied to stent 206. The coating may be applied by injecting, spraying or immersing stent 206 with a liquid coating substance using techniques similar to those described in the background section above. The term "liquid" as used herein refers to substances having sufficient fluidity such that the substance can flow over the surface of stent 206 when processed through the further acts described below. "Liquid" is not intended to limit the coating substance to water-based substances or to low viscosity materials. Even highly viscous substances such as a hyaluronic acid solution (e.g., 1% hyaluronic acid), high molecular weight polyethylene glycol solution, gelatin solution, or poly (lactic) acid in 1, 1, 2 trichloroethane (e.g., 10% poly (lactic) acid) are included within the term.

As occurs with conventional coating techniques, the spraying or immersion of stent 206 in the coating substance typically results in a non-uniform coating, with webbing being observable between struts on stent 206. The term "strut(s)" as used herein includes the elongated elements and interconnecting elements of stent 206. In act 302, the still-wet stent 206 is inserted onto mandrel 204 in centrifuge container 112 such that mandrel 204 extends through the hollow interior of stent 206. Centrifuge container 112 is then inserted into chamber 110 of centrifuge system 100 (FIG. 1), and centrifuge system 100 is used to rotate stent 206 about axis 106 at high speeds. Centrifuge system 100 includes a plurality of

is used, and stent 206 may be implanted immediately after centrifugation act 302. The use of a heating step and the parameters of such a step will vary with the application.

In act 304, it is determined whether one or more additional layers of coating substance is to be applied to stent 206. If so, the process returns to act 301, and another layer of coating substance is applied. Multiple layers of coating substance may be applied to produce a more uniform coating with fewer defects. Each layer can be formed very thin and uniform, and subsequent layers can be added to increase the overall loading onto stent 206. Moreover, the use of multiple layers can provide enhanced control over the release rate of the coating. Finally, when the desired number of layers have been applied, the process is completed at act 305, and stent 206 may be packaged for delivery or immediately implanted into a patient's body using techniques well-known to those of ordinary skill in the art.

In another embodiment shown in Figure 4, act 401 involves applying a first coating substance to a portion of stent 206. As previously described, the coating may be applied by injecting, spraying or immersing stent 206 with an aqueous coating substance using techniques similar to those described in the background section above. In act 402, the still-wet stent 206 is inserted onto mandrel 204 in centrifuge container 112 such that mandrel 204 extends through the hollow interior of stent 206. Centrifuge container 112 is then inserted into chamber 110 of centrifuge system 100 (FIG. 1), and centrifuge system 100 is used to rotate stent 206 about axis 106 at high speeds.

The rotation of chambers 110 at high speeds creates a centrifugal force upon the coating substance that previously was applied to the surface of stent 206. Centrifugal force causes excess accumulations of coating substance, particularly the portions entrained between the struts of stent 206, to be more evenly redistributed over stent 206. Redistribution of the coating substance over the surface of stent 206 provides a more uniform coating free of webbing.

The centrifugation of stent 206 may result in some excess coating substance being removed from the surface of stent 206. Drainage openings 210 are provided in support 202 so that the runoff coating substance can flow from the upper portion of centrifuge container 112 into runoff reservoir 208. The channeling of runoff coating substance into runoff reservoir 208 prevents the coating substance from accumulating at the bottom end 212 of stent 206, which could lead to a non-uniform coating. This runoff coating substance can be

When the desired number of layers have been applied, the process is completed at act 405, and stent 206 may be packaged for delivery or immediately implanted into a patient's body using techniques well-known to those of ordinary skill in the art.

5 The application of one or more coating substances to different portions of the stent or graft precludes potential physical and/or chemical interactions from occurring between multiple substances. In addition, this coating technique also allows variable layers of the same or different substances to be applied to specific portions of the stent, thereby providing enhanced site-specific treatment of various disease states and/or conditions.

10 For example, stents uniformly coated with radioactive materials that limit cell proliferation have been used to treat restenosis. However, one side effect of this treatment method is the occurrence of a "candy-wrapper" effect at the treatment site. In general, the candy-wrapper effect is characterized by enhanced restenosis at the ends or edges of the radioactive stent that cause the ends of the stent to twist and contract in a radially inward direction. The abrupt change in radioactive levels at the edges of the stent, e.g. between
15 tissue contacting the radioactive stent versus tissue not contacting the stent, is thought to further stimulate the proliferation of smooth muscle cells at these sites.

One method of mitigating this effect is to apply variable layers of radioactive material along the surface of the stent. In general, the level or amount of radiation at a tissue site is proportional to the number of layers of radioactive substance applied to the corresponding
20 portion of the stent. As such, gradually decreasing the number of radioactive material layers towards the ends of the stent provides a smooth transition in radiation amounts between adjacent tissue cells. For example, for material delivering a radiation dosage of 10-100 gray (Gy) approximately 1 to 5 layers of material are applied to the central portion of the stent. Successively decreasing numbers of layers of the radioactive material are applied to the stent,
25 terminating at the end or edge portions of the stent having only 1 to 2 layers of material. Other radioactive materials and layer variations, though not expressly disclosed, may also be used. This, in turn, inhibits cell stimulation and proliferation in tissue contacting the stent surface and portions of surrounding tissues, thereby preventing the occurrence of the candy-wrapper effect.

30 Alternatively, materials having different levels of radioactive substances may also be used to counteract the candy wrapper effect. For this embodiment, materials containing

polymer in the composition should be selected such that it is high enough to ensure effective crosslinking of the pre-polymer since a solution too dilute may not form a crosslinked hydrogel. An implantable device may then be dipped into this pre-polymer coating substance. Alternatively, prior to application of the pre-polymer, the implantable device may
5 be perfused with a low surface energy solvent such as, for example, acetone or ethanol, which effectuates improved perfusion of the pre-polymer solution through the interstices of the implantable device.

After the implantable device is dipped into the pre-polymer solution, the implantable device is placed in a centrifuge container and loaded into a centrifuge system, similar to the
10 centrifuge container 112 and centrifuge system 100 described above. Centrifuging the coated implantable device spreads the viscous pre-polymer solution evenly across the surface of the implantable device and into the interstices or crevices therein.

The pre-polymer is cured to form a hydrogel coating on the implantable device. Curing may be accomplished photochemically using ultraviolet or visible irradiation and a
15 photoinitiator, thermally, or by moisture curing at room temperature. The practice of these and other suitable curing procedures is well known to those of ordinary skill in the art.

In yet another embodiment, the coating method of the present invention can be used to provide a physician with greater flexibility in selecting a desired coating substance for use with a particular patient. Conventionally, stents are coated by either the stent manufacturer or
20 a third party prior to delivering the stent to a physician for implantation into a patient. In accordance with the present invention, a physician can apply a coating on a bare stent, centrifuge the stent using a small, portable centrifuge device, and implant the freshly-prepared stent in a patient's body. This enables the physician to precisely select the composition of the coating substance applied to the stent. In addition, because the stent can
25 be locally coated and then immediately implanted by the physician after coating, perishable or environmentally-sensitive materials may be used to coat the stent.

EXAMPLE 1

An ACS Duet® stainless steel stent 206, produced by Guidant Corp. of Indianapolis, IN, is partially dipped or immersed (e.g., for a few seconds or up to 20 seconds or more) in a
30 coating substance composed of BioSpan® (a polyurethane) and Trapidil (i.e., triazolopyrimidine, an antiplatelet) in a 3:1 ratio. The stent 206 is then immediately mounted

EXAMPLE 3

Multi-Link Duet™ stents are cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air-dried. An ethylene vinyl alcohol (EVAL) stock solution is made having an EVAL:DMSO:THF w/w ratio of 1:2:1.5. The mixture is placed in a warm water shaker bath at 60°C for 12 hours. The solution is mixed, then cooled to room temperature. A 5% by weight Actinomycin-D (Ac-D) solution is formulated as follows: 0.95 grams of the EVAL:DMSO:THF solution is mixed with 0.05 grams of AcD. The cleaned Multi-Link Duet™ stents are mounted in a makeshift holder placed within ependorf tubes. One half of the stent is dipped in the EVAL-AcD solution and transferred to the ependorf tube. The dipped end is vertically lower and resting on the holder in the tube. The tube is then centrifuged at 3000 rpm for 60 seconds. The half-coated stent is dried for 2 hours in a vacuum oven at 50°C. Following drying, the clean half of the stent is dipped in Duraflo® (organic soluble heparin) made at 10% w/w in Freon. The coating process is repeated. The final coating configuration results in a one-half AcD and other one-half half Heparin-coated stent.

EXAMPLE 4

Multi-Link Duet™ stents are patterned with microdepots on the outer diameter of the stents. Microdepot stents are cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. A 10% AcD stock solution is made having an AcD:THF w/w ratio of 10:90. A 10% Dexamethasone stock solution is made having a Dexamethasone:THF w/w ratio of 10:90. The cleaned Multi-Link Duet™ stents are mounted in a makeshift holder placed within ependorf tubes. One half of the stent is dipped in the AcD solution and is transferred to the ependorf tube. The dipped end is vertically lower and is resting on the holder in the tube. The tube is then centrifuged at 2000 rpm for 60 sec. The half-coated stent is dried for 1 hour in a vacuum oven at 30°C. Following drying, the clean half of the stent is dipped in the Dexamethasone solution. The coating process is repeated. The drug loaded stents are then coated with Duraflo® solution by spraying a solution of Duraflo® as described in previous embodiments. The final coating configuration results in a one-half AcD and other one-half Dexamethasone coated microdepot stent that is topcoated with Heparin.

Embodiments of the method may also mitigate defects due to handling of the implantable device. In conventional spray processes, the implantable device is held aloft using one or two clamps or fixtures while the coating substance is sprayed onto the device. The point where these clamps contact the device may be masked from receiving the spray, resulting in defects in the coating. In contrast, the centrifuge container 112 has minimal contact with the implantable device during the centrifuge process.

In general, the coating substance of the various embodiments can have a viscosity within the range of about 0.5 cp to 1,000 cp (whereby 1 cp (centipoise) is approximately equal to the viscosity of water at 20°C). As such, 0.5 cp approximately represents a very thin substance, 100 cp approximately represents, for example, a light oil, and 1,000 cp approximately represents a thick, viscous substance. Further, the relationship between the centrifugal force of the centrifuge or similar device and the viscosity of the coating substance can be approximately represented by the following equation:

$$U \sim (g + r \cdot f^2) / k \cdot m$$

Where: U = velocity
 g = gravitational acceleration
 r = average distance $\cdot 4\pi^2$
 f = rpm
 k = surface area to volume ratio (and other geometric constants/parameters)
 m = kinetic viscosity

In addition to the above, the viscosity of the coating substance is also dependent on the type of polymer and concentration of polymer contained in the coating substance.

The above embodiments only illustrate the principles of this invention and are not intended to limit the invention to the particular embodiments described. For example, the heating to evaporate the solvent material may be omitted, and other embodiments utilizing centrifugation coating methods can be used in combination with other acts in different processes which do not require active heating. These and various other adaptations and combinations of features of the embodiments disclosed are within the scope of the invention, as defined by the following claims.

9. The method of claim 2, further comprising heating said implantable device after rotating said implantable device about said axis of rotation.
10. The method of claim 1, wherein said first coating substance or said second coating substance includes a polymer, a solvent, and a therapeutic agent.
- 5 11. The method of claim 10, wherein said polymer is one of the group consisting of: ethylene vinyl alcohol, polyurethane, heparin, polycaprolactone, and poly-lactic acid.
12. The method of claim 10, wherein said solvent is one of the group consisting of: dimethyl sulfoxide, dimethyl formamide, tetrahydrofuran, dimethyl acetamide, and trichloroethane.
- 10 13. The method of claim 10, wherein said therapeutic agent is one of the group consisting of: antinomycin-D, Trapidil, heparin, dexamethasone, and paclitaxel.
14. The method of claim 1, wherein said coating substance contains a crosslinkable pre-polymer, and further comprising:
curing said crosslinkable pre-polymer to form a hydrogel.
- 15 15. An implantable device formed by the method of claim 1.
16. An implantable device formed by the method of claim 2.
17. A drug loaded implantable device comprising two or more coating substances, each of said substances applied to portions of said device.
18. The drug loaded implantable device of claim 17, wherein said portions are
20 exterior surfaces of said device.
19. The drug loaded implantable device of claim 17, where one of said portions is an exterior surface and another of said portions is an interior surface of said device.
20. The drug loaded implantable device of claim 17, wherein one of said substances is a first substance evenly coated on a first portion of said device and another of said substances is a
25 second substance evenly coated on a second portion of said device.
21. The drug loaded implantable device of claim 20, wherein said first portion is a first end of said device and said second portion is a second end of said device.

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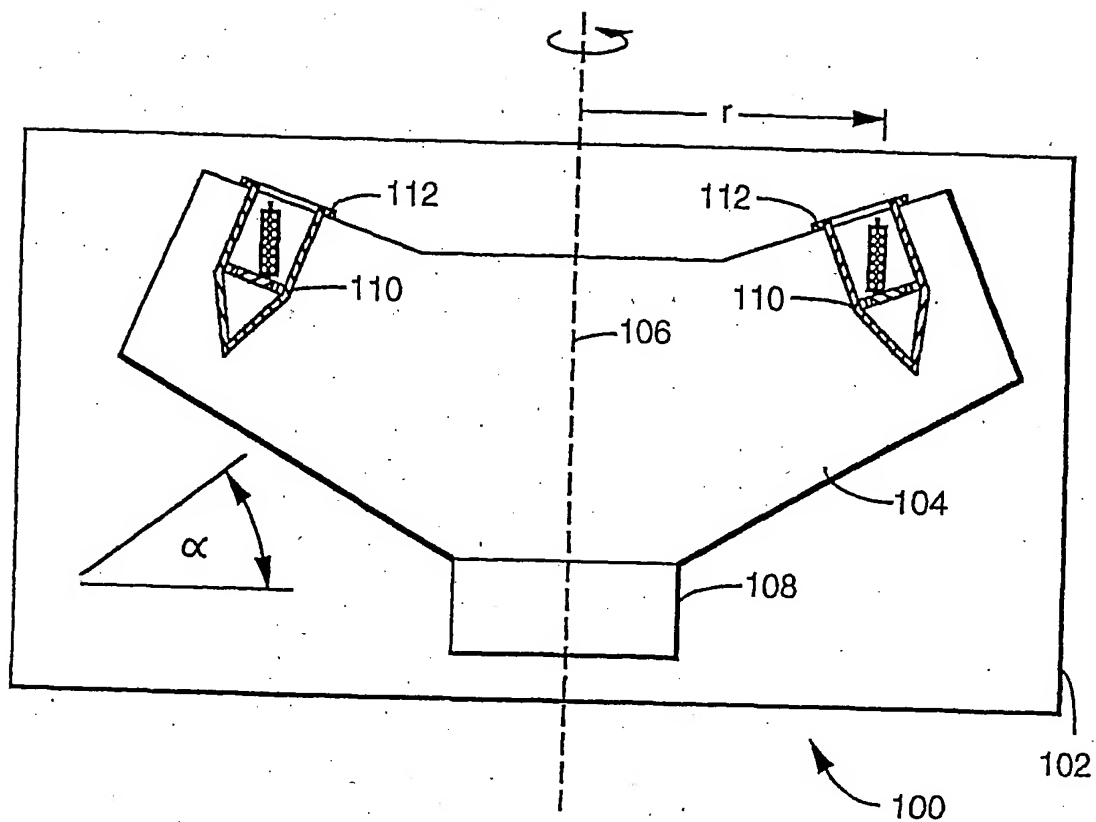


FIG. 1

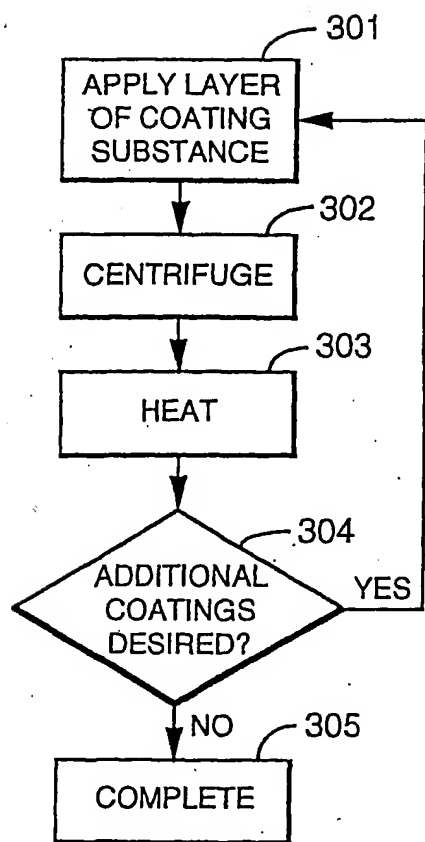


FIG. 3

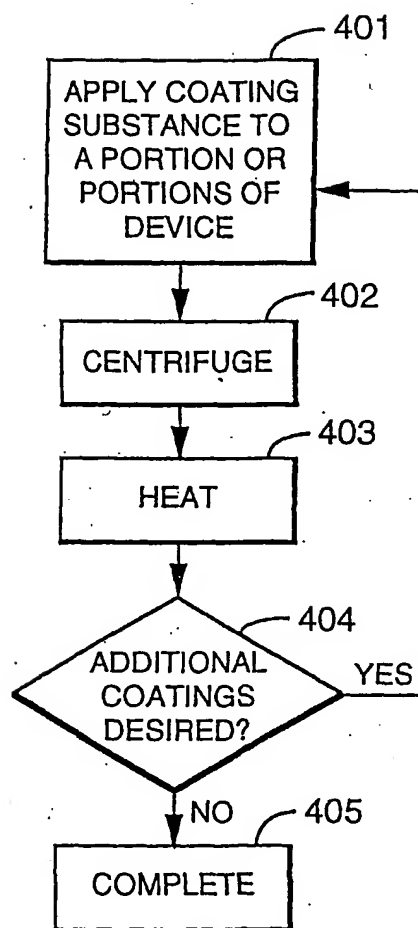


FIG. 4

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